alleged that the specification does not enable the use of the claimed antibodies for diagnosis or therapy. In particular, the Office Action states:

> The specification provides no guidance or objective evidence that the protein to which the instantly claimed antibodies bind is ever expressed, nor is there any guidance or objective evidence that if such a protein were expressed, that it would be expressed at sufficient levels in colon cancer over normal colon tissue and normal non-colon tissues that it would be useful in diagnosis and treatment of colon cancer." *See*, Paper No.12, page 4, second paragraph.

See, Paper No. 12, page 4, second paragraph.

Applicants respectfully traverse and request that the rejection be withdrawn for the reasons explained *infra*. In support of the enablement rejection, the Office Action refers to eight factors set forth in *Ex Parte Forman* (230 U.S.P.Q. 546 (1986)) that are to be considered in determining whether or not a specification is sufficiently enabling without undue experimentation. Applicants assert, however, that in contrast to the situation in *Ex Parte Forman*, the specification in the present case is sufficiently enabling to one having ordinary skill in the relevant field. Moreover, the present case is closely analogous to the situation presented and decided upon in *In Re Wands* (where the court affirmed and opined upon the eight considerations iterated in *Ex Parte Forman). See, In re Wands,* 858 F.2d 731 (1988). In this regard, the M.P.E.P. has also explicitly incorporated the decision in *In Re Wands* as part of the guidelines to be utilized in considering enablement issues:

> *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). In *Wands*, the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. *In re Wands,* 858 F.2d at 736-40, 8 USPQ2d at 1403-07. The Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. After considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to

obtain antibodies needed to practice the claimed invention." *Id.*, 8 USPQ2d at 1407.

M.P.E.P., 8th Ed., § 2164.01(a) (August 2001) (emphasis added).

The present application presents a situation very much like that considered in *In Re Wands* where the specification was found enabling for the claimed antibodies because of the considerable direction and guidance in the specification, the high level of skill in the art, and the well-established methods needed to practice the invention. As discussed below, the present specification does, like *In Re Wands*, provide more than ample guidance to those of ordinary skill in the art for how to make and use the claimed antibodies and methods based thereon.

As of June 6, 1995 (the claimed priority date for the present application), and as pointed out in the present application, methods for making and using a diverse array of antibody types (*e.g.* monoclonal, single-chain, Fab fragments, etc.) were routine for those of ordinary skill in the art. *See e.g.*, specification, page 14, last full paragraph. In this regard, the specification describes various types of antibodies that may be produced against the Colon Specific Protein (*e.g.*, polyclonal, monoclonal, single chain, chimeric, humanized, etc.). *See*, specification at page 36, penultimate paragraph. Additionally, the specification describes various methods by which the antibodies may be produced and directs the reader to instructional resources for the same. *See, e.g.*, specification at page 36, last paragraph to page 37. The specification also describes how Colon Specific Protein may be produced in a bacterial expression system for use in raising, for example, a monoclonal antibody. *See*, specification, Example 2, pages 42-44. The specification also describes and details examples of assays that may be used, such as radioimmunoassays, competitive-binding assays, Western blot analysis, ELISA assays, and "sandwich" assays. *See*, specification, page 14, last full paragraph to page 16, first paragraph. The specification describes how labeled antibodies may be used to detect the Colon Specific Protein. *See*, specification at page 16, second and third paragraph. The specification describes how antibodies may be used to target and destroy colon cancer cells by linking an interaction agent to the antibodies. *See, e.g.*, specification at page 17, first full paragraph. And, the specification even describes how antibodies may be used to carry out *in vivo* imaging to detect a diseased state of colon tissue. *See*, specification at page 17, third paragraph. Hence, Applicants submit that the present

application provided sufficiently ample guidance as of its original filing date in teaching how to make and use the presently claimed antibodies and methods based thereon.

The present Office Action specifically alleges that the specification does not enable the use of the claimed antibodies because they lack utility in diagnosis or therapy of cancer:

> There is no guidance or objective evidence that the instantly claimed antibodies would be useful, because it is not clear that the colon specific protein to which the claimed antibody binds, is expressed in colon cancer cells over normal colon cells, at a level sufficient to produce any therapeutic or diagnostic utility.

See, Paper No. 12, page 4, first full paragraph.

Relatedly, it was also asserted that:

> Those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated.

See, Paper No. 12, pages 4, last paragraph to page 5, first paragraph.

Additionally, three publications (by Shantz et al., McClean et al., and Fu et al.) were cited to illustrate that there is not always a direct correlation between mRNA and protein expression levels. *See*, Paper No. 12, page 5, first paragraph. And, it was also alleged that "one of skill in the art would not be able to predict if SEQ ID NO:1 is in fact translated into the polypeptide of SEQ ID NO:2." *See*, Paper No. 12, page 5, last paragraph.

Applicants respectfully disagree.

The specification teaches that the Colon Specific Gene is overexpressed in colon cancer. *See, e.g.,* specification, page 33, lines 7-8. Further in support of the credibility of the teachings in the present specification, Applicants submit herewith a Declaration by research scientist Adam Bell along with Exhibits A, B, and C. Exhibit A demonstrates the production and characterization (*e.g.*, specificity and useful titer) of polyclonal antibodies that bind to the Colon Specific Protein described in the present application. Exhibit B shows an immunohistochemical stain demonstrating positive Colon Specific Protein antibody binding

(versus control) to normal human colon. Exhibit C shows mRNA over-expression of the Colon Specific Gene in colon and intestinal cancers versus normal colon and intestinal tissues. In particular, the log-scale graph in Exhibit C shows that the Colon Specific mRNA is expressed at a 10-fold higher level in colon adenocarcinoma, as compared to normal colon. Thus, the Declaration of Adam Bell confirms the credibility of the original teachings in the present specification regarding production and overexpression of the Colon Specific Gene and Protein in human colon cancer.

Furthermore, although it is true that mRNA expression levels do not always exhibit a directly proportional correlation with protein expression levels, the lack of at least some general correspondence is the exception rather than the rule. Indeed, the comments in Alberts et al., Shantz et al., McClean et al., and Fu et al. were in fact worthy of publication precisely because they represent exceptions to the norm, not because they are paradigms of the norm. In fact, Alberts et al. also teaches "For most genes transcriptional controls are paramount. This makes sense because of all the possible control points...only transcriptional control ensures that no superfluous intermediates are synthesized." *See*, Alberts et al., Molecular Biology of the Cell, 3rd edition, page 405, last paragraph (1994) (Reiterated in the Summary paragraph, page 404; "Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of RNA transcription is the most important point of control.") (Emphasis added). Hence, when investigating the expression levels of a new gene and protein those of ordinary skill in the art most often look to mRNA expression levels as predictive of the relative protein expression levels. And, as corroborated by Alberts et al., most genes are, in fact, transcribed into mRNA and translated into protein in direct proportion to their relative mRNA expression levels.

Applicants also disagree with the conclusion that "one of skill in the art would not be able to predict if SEQ ID NO:1 is in fact translated into the polypeptide of SEQ ID NO:2." *See*, Paper No. 12, page 5, last paragraph. First, Applicants note that in the four examples cited (Alberts et al., Shantz et al., McClean et al., and Fu et al.) all of the respective mRNAs in question were, in fact, translated into protein (albeit with translation regulated at a post-transcriptional level). Second, as acknowledged by the pending office action, the specification does describe over-expression of the Colon Specific Gene in colon cancer. *See*, Paper No. 12, page 3, last full sentence (referring to the specification at page 33, lines 7-8).

See also e.g., Specification at page 4, first full paragraph. Third, Applicants note that when the present application was originally filed, those of ordinary skill in the art would have expected the Colon Specific mRNA to be translated and expressed as protein. In particular, protein expression would have been expected by those of ordinary skill because, for example, the mRNA encoding Colon Specific Protein exhibits an excellent Kozak consensus sequence for initiation of translation (*i.e.*, with a purine, particularly adenine, at position -3 followed by the hallmark four nucleotide translation initiation sequence (ATGG)). *See*, Kozak, M., Nucleic Acids Research, 15:8125-48 (1987). Moreover, the initiation sequence is also followed by a fairly long open-reading frame which begins with a strong consensus signal peptide sequence (MASRSMRLLLLLSCLAKTGVLG). Furthermore, other investigators have subsequently published on the same Colon Specific Protein amino acid sequence (referred to therein as "Reg IV"), and these investigators have also predicted and inferred protein expression of the Colon Specific Protein mRNA in human colon. *See*, "Isolation and characterization of a cDNA encoding a novel member of the human regenerating protein family: Reg IV," Biochimica et Biophysica Acta, Vol.1518, pp.287-293 (2001).

With respect to scope of enablement, the currently pending office action also indicates:

> It is further noted that should applicant provide evidence that the colon specific protein is expressed, and that antibodies which bind to a colon specific protein might function for diagnosis or treatment of colon cancer, that the claims are not enabled for the broadly claimed antibodies. The claims encompass antibodies which bind minimally to fragments, or portions of the disclosed sequence, and thus encompass antibodies which bind to a broad range of polypeptides, including fragments and variants of SEQ ID NO:2. It is well known in the art that amino acid substitutions have a significant impact on a protein's structure, which would impact the binding and activity of an antibody which binds to that protein. Thus the antibodies as claimed encompass a broad range of antibodies which would bind to a highly variant group of proteins and which would therefore induce highly different therapeutic and diagnostic effects.

See, Paper No. 12, page 6, last paragraph to page 7, first paragraph.

Applicants respectfully disagree with these assertions. Although the pending claims do encompass antibodies which <u>specifically bind</u> to <u>fragments</u> of SEQ ID NO:2, the presently

pending claims do not recite antibodies that bind to variants of SEQ ID NO:2. Hence, in contrast to the asserted rejection, Applicants submit that the antibodies of the present claims do not "bind to a highly variant group of proteins." Instead, the pending claims encompass antibodies that bind with specificity to polypeptides of SEQ ID NO:2 or to polypeptides encoded by the cDNA of the ATCC Deposit. Accordingly, the Applicants respectfully submit that one of ordinary skill in the art was quite readily enabled to make and use the claimed antibodies and methods as of the original application filing date.

Hence, for the reasons discussed above, Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 U.S.C. §112, Written Description

Claims 21, 23-37, 46, 48-50, 73, 75-89, 98 and 100-102 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." *See*, Paper No. 12, page 9, first paragraph.

In particular, the outstanding office action asserts:

> The claims are broadly drawn to an antibody which binds to a polypeptide of any size comprising a sequence that minimally contains portions of SEQ ID NO:2, or the protein encoded by the cDNA contained in ATCC deposit #97129...Thus the claims are drawn to a large genus of molecules...The specification discloses only the structural features of one species, the polypeptide of SEQ ID NO:2. The specification lacks information to lead one of ordinary skill in the art to understand that the applicant had possession of the broadly claimed genus of antibodies at the time the instant application was filed. Applicant is referred to the guidelines for 112, first paragraph, published in the Official gazette and also available on www.uspto.gov.

See, Paper No.12, page 9, last paragraph.

Applicants respectfully traverse and request that the rejection be withdrawn for the reasons explained *infra*.

Applicants submit that the present specification provided ample information to lead one of ordinary skill in the art to understand the Applicant had possession of the claimed

genus of antibodies. The present specification describes more than just antibodies which bind to the polypeptide of SEQ ID NO:2. The specification describes that the present invention encompasses antibodies which bind to, *inter alia*, immunogenic polypeptide fragments, 30 amino acid polypeptide fragments, and 50 amino acid polypeptide fragments (*see e.g.*, Specification, at page 36, fourth paragraph, and at page 19, first full paragraph). However, it is important to recognize that all the instant claims require that the antibody specifically binds to an amino acid sequence which is some portion of SEQ ID NO:2. One of ordinary skill in the art would readily recognize whether or not any given polypeptide to which an antibody binds constitutes an immunogenic fragment, a polypeptide comprising 30 amino acids, or a polypeptide comprising 50 amino acids of the polypeptide sequence of SEQ ID NO:2 or the polypeptide encoded by the cDNA in ATCC Deposit No. 97129.

Thus, the genus of claimed antibodies has been fully described. Accordingly, Applicant respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the remarks above be entered and made of record in the file history of the instant application.

Respectfully submitted,

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Lin J. Hymel, Reg. No. 45,414
Attorney for Applicants

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850
Phone 301-251-6015

MMW/LJH/DAS/rmr